I. Rejections Under 35 U.S.C. § 112

In the Office Action, the Examiner maintained his rejection of the pending claims on the grounds of non-enablement, stating that "the specification, while enabling for a controlled release oral solid dosage form comprising a core of an alkyl ester of a hydroxy substituted naphthalene compound, a pharmaceutically acceptable, water swellable polymer and an osmotic agent and an outer coating layer which completely covers the core comprising a pH sensitive coating agent and a water insoluble polymer used at a weight ratio of about 0.1:1 to 0.75:1 at a combined coating weight of 0.5-5% by weight, does not reasonably provide enablement for a controlled release oral solid dosage formulation without the recited limitations regarding a core and an outer coating having the weight ratio and combined coating weight has been maintained for reasons of record in paper number 2, paragraph 2."

In the maintained reasons of rejection from paper number 2, paragraph 2, the Examiner states that "[t]he limitation . . . regarding the core and the coating as well as the ratio of pH sensitive polymer to insoluble polymer and the total weight used ***are critical*** to the invention because the ratios and weights falling significantly outside these boundaries will not have the required dissolution properties and with out [sic] the outer coating of the core the composition will not be controlled release" (Emphasis added).

The Examiner's rejection based on enablement is respectfully traversed. As will be explained in detail in the following paragraphs:

- there is no ***limitation*** regarding the core and the coating anywhere in the claims;
- there is ***no criticality*** attributed to *any* specific dosage form in the specification or in the claims;
- the specification provides detailed information concerning formulation technologies that are useful in connection with the presently claimed controlled release oral solid dosage forms;

- there is ***no basis*** under §112 for the Examiner to require the claims to be limited to the exemplified embodiments; **and therefore**
- the Examiner's rejection based on a purported lack of enablement must be removed.

1. Case Law (The Test for Enablement)

It is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); MPEP 2164.01 (8th Edition). In the present case, applicants have provided in the specification formulations, methods of making the formulations and clinical studies of these formulations that support the limitations (e.g., T_{max} values) recited in the present claims.

A. Exemplified Formulations

Examples 1 and 2 of the present application are directed to a tablet formulation containing lovastatin in the tablet, an inner coating containing hydroxypropylmethylcellulose phthalate 55 and an outer coating containing cellulose acetate. Example 3 of the present application is directed to a tablet formulation containing lovastatin in the tablet, an outer coating containing cellulose acetate and an overcoat containing hydroxypropylmethylcellulose phthalate 55. Example 4 of the present application is directed to a tablet formulation containing lovastatin in the tablet, and an outer coating containing cellulose acetate. Examples 5-9, similar to Examples 1 and 2 contain lovastatin in the tablet, an inner coating containing hydroxypropylmethylcellulose phthalate 55 and an outer coating containing cellulose acetate.

Clinical studies were conducted to evaluate the formulations of Examples 5-9, and are set forth in the specification on pages 40 -55. These clinical studies provide objective enablement of the claimed formulations.

"Nothing more than objective enablement is required, and therefore, it is irrelevant whether [a] teaching is provided broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Clearly in this instance the Examiner is attempting to limit applicants to the exemplified embodiments set forth in the specification, and is ignoring the significant amount of disclosure in the specification which directs one of ordinary skill in the art how to make the claimed formulations using other well-known controlled release technologies, without undue experimentation.

2. Enablement/Scope of the Claims

"Limitations and examples in the specification do not generally limit what is covered by the claims." MPEP 2164.08 (8th Edition); *Lucas Aerospace*, 890 F. Supp. at 332 (citing *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 987 (Fed. Cir. 1988)). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); MPEP 2164.10 (8th Edition).

The present claims should not be limited to the examples. Once having been provided with the information set forth in the present specification (e.g., controlled release oral solid dosage forms for the reduction of serum cholesterol levels which provide a T_{max} which occurs at from about 10 to about 32 hours after oral administration, and which is administrable on a once-a-day basis to human patients, and described in the detail set forth in the specification (exemplified in-vivo results which support the claims; detailed description of how to make the exemplified formulations; detailed description of how to make such formulations which possess the claimed parameters using other controlled release technologies)), one of ordinary skill in the art having the information contained in the specification would without undue experimentation be able to manufacture formulations falling within the claims via other controlled release technologies such as those discussed in detail in the specification.

The specification in no uncertain terms states that other controlled release technologies beyond that exemplified can be used, and provides sufficient guidance to one skilled in the art to manufacture such alternative formulations without undue experimentation.

In addition, the case law does not require each possible formulation encompassed by the claims to be exemplified. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 84 (CCPA 1970); MPEP 2164.01(b) (8th Edition) ("As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."). "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation" MPEP 2164.02.

Therefore, the Applicants are not required to exemplify every formulation which would be encompassed by the claim. If the application provides sufficient guidance for one of ordinary skill in the art to manipulate formulations proposed by the disclosure of the present application then the claim is enabled.

In the present application, Applicants are claiming a controlled release oral solid dosage form comprising an alkyl ester of hydroxyl substituted naphthalenes and a controlled release carrier providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at about 10 to about 32 hours after oral administration. Applicants have provided certain representative examples of these formulations in the present application, and have stated in the specification that a number of controlled release technologies useful in accordance with the present invention.

Further, the prior art is replete with controlled release technology and, as stated in the present application, an abundance of controlled release technologies can be used to manufacture the results that Applicants have attained in the present invention.

3. Non-criticality of Formulation Components

"In determining whether an unclaimed feature is critical, the entire disclosure must be considered." MPEP 2164.08(c) (8th Edition). "Features which are merely preferred are not to be considered critical." MPEP 2164.08(c) (8th Edition) (*citing In re Goffe*, 542, F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)). "[A]n enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended," and "[b]road language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality." MPEP 2164.08(c) (8th Edition).

The parameters mentioned by the Examiner are not "critical". Our specification does not state or suggest that parameters mentioned in the Office Action by the Examiner are critical; on the contrary, throughout the present application, various controlled release technologies are discussed which can be modified by those of ordinary skill in the art to provide a mean time to maximum concentration (T_{max}) of an alkyl ester of a hydroxy substituted naphthalene which occurs at about 10 to about 32 hours after administration.

In addition, no where is it stated that it is critical to only use the exemplified dosage forms. To the contrary, it is specifically contemplated that the use of the exemplified dosage forms is not critical. In support of this position, the Examiner is directed to page 19, line 36 of the application which discloses the following:

> **Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present**

> **invention**, i.e., formulations which provide a mean Tmax of the drug (i.e., a HMG-CoA reductase inhibitor) at the desired time after oral administration, e.g., in general, at about 10 to about 32 hours after oral administration to a population of human patients, and which preferably provide other pharmacokinetic parameters described herein when orally administered to human patients. **Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art.** In either case, the controlled release dosage form may optionally include a controlled release carrier which is incorporated into a matrix along with the drug (e.g., HMG-COA reductase inhibitors), or which is applied as a controlled release coating.

(Emphasis added).

With respect to this basis of rejection, it is respectfully submitted (consistent with the Applicant's position above) that the limitations of the exemplified dosage form as presented by the Examiner are not critical to the invention.

Further, it appears that the Examiner is stating that a coating is required in order to provide a sustained release of an alkyl ester of a hydroxy substituted naphthalene to provide a mean (T_{max}) which occurs at about 10 to about 32 hours after administration. This is also not a critical limitation as the prior art is replete with controlled release technologies which comprise an active agent in a matrix, without the need for a further coating, which can be used to achieve the present invention with the benefit of hindsight provided by the present application.

In view of the above discussion, it is respectfully submitted that applicants are entitled to the full and proper scope of their claims, and that the Examiner's rejection under §112 should be removed. If, however, for some unknown reason the Examiner intends to maintain his position that one skilled in the art having the information contained in the specification is not sufficient to enable one of ordinary skill in the art to manufacture a controlled release formulation within the claims, then it is respectfully suggested that the Examiner set forth his reasoning in a duly executed declaration under MPEP § 2144.03 (8th Edition). Of course, this fact will be disputed.

It is respectfully noted that the Examiner, in making a convoluted rejection under 35 U.S.C. §103, *has already taken the position that one of ordinary skill in the art of pharmaceutical manufacturing having the knowledge of the present specification and claims, could then manufacture a controlled release formulation having the claimed parameters using a* ***different system*** (e.g., as set forth in Alberts et al. or the Oshlack et al. references) and achieve the claimed formulations.

As provided above, it has been demonstrated that

1. Applicants have provided representative examples of the formulations claimed.
2. Applicants are not required to exemplify every formulation encompassed by the claims.
3. The specification provides that other controlled release technologies beyond that exemplified can be used, and provides sufficient guidance to one skilled in the art to manufacture such alternative formulations without undue experimentation
4. The features mentioned by the Examiner are not critical to the invention.

Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. §112 rejection of the pending claims.

II. Rejections Under 35 U.S.C. § 103

In the Office Action, the Examiner rejected the pending claims under 35 U.S.C. 103(a) "as being unpatentable over Alberts et al. (U.S. Patent No. 4,997,658)." It appears that the Examiner's rejection over Alberts et al. is in combination with Oshlack et al. (which applicants assume to be U.S. Patent No. 5,324,351 or 5,472,712 as indicated in the previous office action). The Examiner stated that "Alberts et al. discloses an alkyl ester of a hydroxy substituted naphthalene derivatives, including lovastatin, which is a medicament used in lowering the plasma cholesterol level in a subject by time-controlled administration (see entire document)." The Examiner notes that "Alberts et al. does not disclose materials that are similar or the same as

those of used in the instant claimed invention." However, the Examiner states that "Oshlack et al. discloses structural components as well as compositions used to overcoat active agent including pharmaceuticals (see Abstract and entire document)" and "[t]he advantage of the overcoat is to protect from the environment." The Examiner concludes that "it would have been obvious to one of ordinary skill in the art to use the coating compositions disclosed by Oshlack et al. in the invention of Alberts et al. to obtain an active ingredient that is protected from the environment to provide stability in the absence of a factual showing to the contrary or a showing of unexpected result."

This rejection is respectfully traversed. Although the present claims do not preclude a coating which provides stability of the dosage forms and methods thereof, it appears that the Examiner is basing his rejection on a particular structural species (a coating which provides stability to an active agent) which may be encompassed by the structural genus of the claims (a controlled release carrier which may or may not provide stability to the recited agent). However, it is submitted that the rejection is not directed to the recited functional limitations of the structure, i.e., a mean (T_{max}) of an alkyl ester of a hydroxy substituted naphthalene which occurs at about 10 to about 32 hours after administration. Accordingly, it is respectfully submitted that the Examiner has not presented a *prima facie* case of obviousness based on the rejection presented and the rejection should be withdrawn.

It is respectfully submitted that there is no motivation to combine Alberts et al. with the Oshlack et al. patents.

Alberts et al. do not mention the use of aqueous dispersions of ethylcellulose, such as those utilized in the Oshlack, et al. patents. Albert et al. use organic solvents and dissolve cellulose acetate therein and spray the resulting solution (see, e.g., column 7 , lines 31-40) onto the cores. Because Alberts et al. utilize an **organic-based** solvent, there is no stability problem such as that identified in the Oshlack, et al. patents. On the other hand, the Oshlack, et al.

patents are directed to the problems associated with the use of **aqueous based** solvents to create ethylcellulose **dispersions** (not solutions where the ethylcellulose is dissolved). Oshlack et al. identify the problem as a lack of stability for formulations coated with a polymer coating derived from an aqueous-based dispersion of hydrophobic polymer, and their solution is to **cure** the coated formulation.

In view of the fact that the Alberts, et al. formulations do not suffer from the problem solved by the Oshlack, et al. patents, there is absolutely no motivation to combine these references. Furthermore, even if one did combine the references, one does not then arrive at the present invention. At best, one would merely modify the Alberts, et al. organic based coatings and instead utilized aqueous-based cured coatings.

Furthermore, the Examiner is reminded that the thereapeutic agents required in the presently claimed formulations, alkyl esters of hydroxy substituted napthalenes, ***are not even*** mentioned in the Oshlack et al. patents at all.

Neither Alberts et al., nor the Oshlack et al. patents cited by the Examiner alone or in combination teach, hint or suggest dosage forms and methods which provide a mean (T_{max}) at about 10 to about 32 hours after oral administration as recited in the independent claims of the present invention. The only T_{max} values even mentioned in either Alberts et al. or the Oshlack et al. references are in the examples of Oshlack et al. **directed to a wholly different class of therapeutic agents (opioid analgesics)** wherein the T_{max} values recited are less than 10.

In view of the above, the Examiner is respectfully requested to remove the rejection over the Alberts et al. patent and the Oshlack et al. patents.

III. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance.

It is noted that this response is accompanied by a three month petition for extension of time under 37 CFR § 1.136(a) and authorization to charge our deposit account for the requisite fee.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Clifford M. Davidson
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940